B4 C5 interacting with tumor/host communication pathways.

REMARKS

Status of the claims

Claims 12-28 are pending in the application.

Claim 23 has been withdrawn from consideration.

Claims 12-22 and 24-28 have been rejected. Claims 12-22 and 24-28 have been rejected under 35 U.S.C. §112, first and second paragraph. Claims 12-16, 18, 20 and 26 have been rejected under 35 U.S.C. §102. Claims 12-16, 18, 20, 22 and 26 have been rejected under 35 U.S.C. §103. Claims 17, 19, 21, 24, 25, 27 and 28 are deemed free of the prior art.

By way of this amendment, claim 23 has been canceled without prejudice, claims 12, 19 and 21 have been amended and new claims 29-32 have been added.

Upon entry of this amendment, claims 12-22 and 24-32 will be pending.

Summary of the Amendment

The claims have been amended to more clearly define the invention, to place some claims in independent form and to further define specific embodiments.

Claim 12 has been amended to eliminate the term "capable of expressing" with the term "that expresses." Support for the amendment is found throughout the specification. No new matter has been added.

Claims 19 and 21 have been amended to place the claims in independent form. Claim 19 has been amended by adding the limitations in claim 12, the claim from which it depends, into claim 19. Claim 21 has been amended by adding the limitations in claims 12 and 18, the claims from which it depends, into claim 21. Support for the amendment is found throughout the specification and claims as filed. No new matter has been added.

New claims 29 and 30 are new method claims which depend on claim 27. New claim 29 refers to specific methods in which the molecule produced by the producer cells is selected from a group of particular species. New claim 30 refers to specific methods that use compositions that comprise a producer cell that is encapsulated in a bead or microbead and the alginate concentration within the bead or microbead increases from the center of the bead or the microbead to the outer rim. Support for new claims 29 and 30 is found throughout the specification and claims as filed. No new matter has been added.

New claim 31 is a composition claim that is dependent on claim 22 and refers to a specific molecule produced by the producer cells selected from a group of particular species. Support for new claim 31 is found throughout the specification, particularly page 6, lines 27 and 28. No new matter has been added.

New claim 32 is a composition claim that is dependent on claim 12 and refers to producer cells that contains a plasmid which include a nucleic acid sequence that encodes a protein that is capable of interacting with tumor/host communication pathways. Support for new claim 32 is found throughout the specification, particularly page 28, line 20 to page 30, line 10. No new matter has been added.

Rejections under 35 U.S.C. §112, first paragraph

Written Description

The Specification Describes the Claimed Subject Matter

Claims 12-22 and 24-28 have been rejected under 35 U.S.C. §112, first paragraph, because it is asserted that the claims contain subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, was in possession of the claimed invention. Specifically, it is asserted in the paragraph bridging pages 2 and 3 of the Official Action that the specification allegedly describes only a single species, endostatin, of the claimed genus of molecules that

inhibit the growth of CNS tumors and affect neovascularization. The Official Action states that "In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any other CNS tumor growth inhibitor that affects neovascularization. Applicants respectfully traverse the rejection.

The specification is in full compliance with the written description requirement and describes a representative number of species of the claimed genus. "The issue of whether a patent specification adequately describes the subject matter claimed is a question of fact. *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996) citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2D (BNA) 1111, 1116 (Fed. Cir. 1991). A genus may be adequately described through description of a representative number of species that comprise the genus. *Regents of the Univ. of Calif. v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997); M.P.E.P. § 2163. When substantial variation exists within the genus, a sufficient variety of species must be described to reflect the variation within the genus. M.P.E.P. § 2163.

In the instant application, contrary to the assertions in the Official Action, the specification in fact describes more than a single species. That is, the specification describes a representative number of species that comprise the claimed genus of molecules that inhibit the growth of CNS tumors and affect neovascularization. Specifically, the specification describes on page 6, lines 25-28, producer cells as those cells that produce proteins and peptides that affect tumor neovascularization, including thrombospondin, endostatin, angiostatin, and prolactin. Applicant respectfully asserts that this portion of the specification clearly sets forth four species of molecules, not simply a single species as asserted in the Official Action.

The specification, therefore, describes a representative number of species that reflect the variation within the presently claimed genus of molecules that inhibit the growth of CNS tumors and affect neovascularization. The specification contains an adequate written description of the claimed subject matter, and the application is in compliance with the requirements of the first

paragraph of section 112. Applicants respectfully request withdrawal of the rejection.

Enablement

The Specification Fully Enables the Claimed Subject Matter

Claims 12-22 and 24-28 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an encapsulated producer cell that expresses a molecule that inhibits the growth of CNS tumors and affects neovascularization in rats, allegedly does not provide enablement for an encapsulated producer cell that expresses a molecule that inhibits the growth of CNS tumors and affects neovascularization in any animal. Applicants respectfully disagree. The specification enables those of ordinary skill in the art to make and use the full scope of the subject matter defined by the claims without undue experimentation.

The enablement requirement is met if the specification enables those of ordinary skill in the art to make and use the subject matter defined by the claims without undue experimentation. *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976). Extensive experimentation is often necessary to practice inventions that involve unpredictable technologies, and such experimentation is not undue. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The Office Action acknowledges that the specification is enabling for an encapsulated producer cell that expresses a molecule that inhibits growth of a CNS tumor and that affects neovascularization in rats. If the skilled artisan wished to make and use encapsulated producer cells that express growth inhibitors of CNS tumors and that affect neovascularization in organisms other than rats, he or she need only review the specification and follow the abundant direction provided therein.

The experimentation required to prepare and use encapsulated producer cells that express molecules that inhibit the growth of CNS tumors and that affect neovascularization in any organism susceptible to such tumors would not be undue and would not require ingenuity beyond that expected of one skilled in the art. For example, the specification provides extensive

teachings regarding how to make producer cells encapsulated in non-immunologically activating alginate. See, for example, page 9, line 26 to page 12, line 17 and page 22, line 17 to page 23, line 32 of the specification as filed. The specification further teaches that the encapsulated tumor cells can be placed into a tumor cavity following surgery in which a tumor has been removed, and describes such procedures. See, for example, page 12, line 19 to page 13, line 11 of the specification as filed. The specification also teaches procedures that can be used to determine the particular types of producer cells that can be used to treat CNS tumors. See, for example, page 13, lines 13 to 22 of the specification as filed. The specification further describes appropriated dosages of implanted producer cells. See, for example, page 13, line 28 to page 14, line 5 of the specification as filed.

The Official Action refers to Visted et al. as providing evidence of the unpredictability of the art. Applicant disagrees. Applicant is a co-author in Visted et al. which describes the problems in the field solved by the present invention. For example, the reference to the failure of gene therapy vectors disclosed in Visted et al. is provided to introduce the improvement that is the claimed invention - i.e., producer cells, as an alternative to gene therapy. By using cells that produce the desired molecule, the present invention solves the problem described in Visted et al. Similarly, the Official Action refers to Visted et al. as evidence of unpredictability because Visted et al. indicates that alginates with >85% M content invoke immune reactions. The claimed invention clearly indicates that the G content is at least 15%, therefore the M content cannot be >85%. Accordingly, the problem referred to in Visted et al. is solved by the claimed invention. The Official Action relies upon Visted et al. to support the contention that the invention is unpredictable because of possible immune reactions against the implant and of possible fibrotic overgrowth of the implant. As pointed out in the specification, the alginate purity and content is specifically chosen to prevent immune responses (page 10, lines 11-28). Likewise, the specification points out on page 42, lines 9-16, that due to the unique location and the lack of fibroblasts in the CNS, fibrotic overgrowth was not observed using the present

invention. Visted et al. is also referenced as indicating unpredicability due to immunoglobulin production against the cells and cell products. Visted et al., however, goes on to refute this position, indicating that "the location of the implant may be important to circumvent the host's immune response. The CNS may actually represent a suitable site for implantation because of its specific immunologic status. The immune responses of the CNS are mainly cellular and the alginate provides a barrier against cell mediated (lymphocyttes, natural killer cells or microglia) destruction of the producer cells." Accordingly, Visted et al. mentions the problem of immunoglobulin production against the cells and cell products as being a problem for other implants but not for the CNS. The other reasons cited for asserting unpredicability in the art with reference to Visted et al. as support, are not sufficient to establish unpredictability. With respect to whether or not large animals can tolerate the claimed invention as well as small animals, no evidence is provided that suggests large animals would not. Visted et al. merely indicates that large animal testing are a prerequisite to clinical trials. There is no suggestion that one skilled in the art would not expect the claimed invention to work, merely a suggestion of how development toward an approved human therapy should proceed. Similarly, the reference in Visted et al. to a theoretical elicitation of glial response that might abolish therapeutic benefit does not rise to the level of evidence that one skilled in the art would not expect the claimed invention to work. Rather, Visted et al. merely sets forth a theoretical possibility which did not occur in rats and which is not indicated to be more likely in other species. Finally, the lack of data on toxicity of alginates in large animals and the fact that clinical trials have yet to occur do not indicate that the one skilled in the art would not expect the claimed invention to work nor provide any basis to question the enablement of the claimed invention.

The specification provides working examples that demonstrate that alginate-encapsulated producer cells survive and proliferate for long periods of time *in vitro* and *in vivo*. See, for example, page 24, line 1 to page 25, line 15; page 31, line 11 to page 32, line 8; page 34, line 13 to page 35, line 16; and page 37, lines 1-17 of the specification as filed. The

working examples also demonstrate that gene products such as endostatin are produced by encapsulated producer cells during several weeks of *in vitro* cell culture and substantial amounts of endostatin is released from the beads. See, for example, page 28, line 20 to page 30, line 10 and page 36, lines 24-31 of the specification as filed. The working examples also teach that encapsulated hybridoma cells produce and release, *in vitro* and *in vivo*, large amounts of a mouse monoclonal antibody that binds to and blocks the EGF-binding domain of the human epidermal growth factor receptor. See, for example, page 36, line 15 to page 27, line 29 and page 36, lines 1-11 of the specification as filed. The specification further teaches that such antibodies inhibit the migration of human GaMg tumor cells, which express the EGF receptor. See, for example, page 28, lines 1-15 and page 36, lines 13-22 of the specification as filed.

In addition, the specification teaches that encapsulated hybridoma cells implanted into rat brains produce and release monoclonal antibodies within the rat brain, and the antibodies disseminate within the brain parenchyma, as well as within the subarachnoidal and in the perivascular space. See, for example, page 30, line 15 to page 32, line 9 and page 37, line 1 to page 38, line 12 of the specification as filed. The specification further teaches that a low immune response towards alginate encapsulated cells occurred within the brain, with only some microglial cells assembling in the brain tissue close to the implanted beads. See, for example, page 32, line 15 to page 33, line 9 and page 38, line 17 to page 39, line 12 of the specification as filed. In addition, the specification teaches that when the brains of rats were implanted with gliosarcoma cells and endostatin-producing 293 cells, large necrotic areas in the tumors were observed, and rats that received the endostatin-producer cells lived significantly longer than rats that were treated with mock transfected cells. See, for example, page 33, line 14 to page 34, line 7 and page 39, lines 15 -25 of the specification as filed.

The specification's teachings, therefore, are not limited to encapsulated producer cells that express an inhibitor of the growth of a CNS tumor and that affect neovascularization in rats, as asserted in the Office Action. To the contrary, the specification teaches *in vitro* experiments

in which the migration of a ***human*** tumor cell line was inhibited by monoclonal antibodies produced from an encapsulated hybridoma cell line. The specification further correlates the *in vitro* results with *in vivo* activity and demonstrates that encapsulated hybridoma cells implanted into rat brains produce and release monoclonal antibodies within the rat brain. Furthermore, the specification teaches that encapsulated 293 cells transfected with an episomal expression vector containing the gene encoding human endostatin released substantial amounts of endostatin during *in vitro* cell culture. Again, the *in vitro* results were correlated with *in vivo* activity through experiments demonstrating that the producer cells caused necrosis of gliosarcoma cells in rat brains. The specification thus provides extensive teachings that allow those of ordinary skill in the art to make and use any embodiment encompassed by the claims without undue experimentation.

The Office Action asserts that "since determination of the efficacy of the encapsulated cell therapy would require, initially, large animal studies before the clinical trials...After experimentation in the large animal model(s), the efficacy of the treatment would have to be tested in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps." (Office Action dated March 29, 2002, page 7). Applicants are not required to demonstrate the "efficacy of the treatment" in large animals or in humans to enable the claimed subject matter. The Office Action seems to require that Applicants perform the testing necessary for FDA approval to satisfy the enablement requirement. Applicants refer to MPEP § 2107.03, which states that:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. . . . [I]t is improper for Office personnel to request evidence . . . regarding the degree of effectiveness [in humans] (underlining in original).

Enablement requires only that the specification provide adequate guidance as to how to make and use the invention without undue experimentation. Those having ordinary skill in the

art would be able to practice the present invention without undue experimentation by following the extensive teachings provided in the specification. Accordingly, the enablement requirement has been satisfied and Applicants request withdrawal of the rejection.

The claims are in compliance with the requirements of 35 U.S.C. §112, first paragraph. Applicant respectfully requests that the rejections of claims 12-22 and 24-28 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 12-22 and 24-28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the term "capable" in claim 12 is deemed vague.

Applicant has amended claim 12 to delete this term and the rejection is moot. As amended, the claims are clear and definite and particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully requests that the rejection of claims 12-22 and 24-28 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. §102

Claims 12-16, 18, 20 and 26 have been rejected under 35 U.S.C. §102 as being anticipated by Skjak-Braek et al. (U.S. Patent 5,459,054). This rejected is promulgated on the interpretation of the claim with the term "capable" such that the claim does not require the producer cell to actually produce the molecule recited in the claim.

Claim 12 has been amended to delete this objectionable term and the rejection is moot. As amended, the claims define subject matter which is neither disclosed nor suggested by Skjak-Braek. Applicant respectfully requests that the rejection of claims 12-16, 18, 20 and 26 have been rejected under 35 U.S.C. §102 be withdrawn.

Rejections under 35 U.S.C. §103

Claims 12-16, 18, 20, 22 and 26 have been rejected under 35 U.S.C. §103 as being obvious over Skjak-Braek et al. (U.S. Patent 5,459,054) in view of O'Reilly (Cell).

Skjak-Braek describes alginate-encapsulated cells but does not describe or suggest producer cells that actually produce the molecule recited in the claims. O'Reilly describes endostatin and its production in recombinant cells. It is asserted that it would have been obvious to combine the teachings of Skjak-Braek and O'Reilly to produce alginate-encapsulated cells that produce endostatin as claimed in claims 12-16, 18, 20, 22 and 26. Applicants respectfully disagree.

Skajak-Braek neither teach nor suggest the use of implanted alginate-encapsulated cells to treat CNS tumors and the particular advantages of using such technology with respect to the physiology and immunological considerations associated with the CNS and CNS tumors. O'Reilly discloses delivering endostatin using a subcutaneous depot and does not suggest that combination of references. O'Reilly does not teach or suggest any advantages in using endostatin to treat primary CNS tumors.

The combination of Skajak-Braek and O'Reilly neither teach nor suggest the invention as claimed in claims 12-16, 18, 20, 22 and 26. Applicant respectfully requests that the rejection of claims 12-16, 18, 20, 22 and 26 have been rejected under 35 U.S.C. §103 be withdrawn.

Conclusion

Claims 12-22 and 24-32 are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Mark DeLuca
Registration No. **33,229**

Date: July 29 2002

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 23 has been canceled.

Claims 29-32 have been added.

Claims 12, 19 and 21 have been amended as follows:

12 (Amended). A composition comprising a producer cell <u>that expresses</u> [capable of expressing] a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, wherein the molecule is: [(a)] a molecule that is capable of interacting with tumor/host communication pathways. [; or

(b) a monoclonal antibody capable of interacting directly with an antigen of the CNS tumor selected from the group consisting of platelet derived growth factor receptors AA and BB, acidic and basic fibroblast growth factor receptors, transforming growth factor receptorsalpha and beta, vascular endothelial growth factor receptors, tyrosine kinase receptors with immunoglobulin-like and EGF-like domains, hepatocyte growth factor, CD-44, CDR/cyclincomplexes, glycolipids on the cell surface, glycoproteins, and proteins derived from the expression of oncogenes.]

19 (Amended). <u>A</u> [The] composition <u>comprising a producer cell that expresses a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, wherein the molecule is a molecule that is capable of interacting with tumor/host communication pathways.</u>

[according to claim 12,] wherein the CNS tumor is a brain tumor.

21 (Amended). A [The] composition comprising a producer cell that expresses a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, wherein the molecule is a molecule that is capable of interacting with tumor/host communication pathways, [according to claim 18,] wherein the producer cell is encapsulated in a bead or microbead and the alginate concentration within the bead or microbead increases from the center of the bead or the microbead to the outer rim.

29 (New). The method according to claim 27 wherein the molecule that is capable of interacting with tumor/host communication pathways is a molecule capable of affecting tumor neovascularization selected from the group consisting of: thrombospondin, endostatin, angiostatin, and prolactin.

30 (New). The method according to claim 27 wherein the wherein the producer cell is encapsulated in a bead or microbead and the alginate concentration within the bead or microbead increases from the center of the bead or the microbead to the outer rim.

31 (New). The composition according to claim 22 wherein the molecule that is capable of affecting tumor neovascularization is selected from the group consisting of: thrombospondin, endostatin, angiostatin, and prolactin.

32 (New). The composition according to claim 12 wherein the producer cell comprises a plasmid that includes a nucleic acid sequence that encodes a protein that is capable of interacting with tumor/host communication pathways.